Characterization of early-onset SARS-CoV-2 infection in immunocompromised patients who received tixagevimab-cilgavimab prophylaxis

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Abstract

Tixagevimab-cilgavimab is authorized for pre-exposure prophylaxis against coronavirus disease 2019 (COVID-19) in immunocompromised hosts. Herein, we report the clinical characteristics of eight patients who developed COVID-19 soon after receiving tixagevimab-cilgavimab. This study emphasizes the need to maintain additional measures to prevent COVID-19 during periods of high SARS-CoV-2 transmission.

Introduction

Since the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late December 2019, the number of patients developing coronavirus disease 2019 (COVID-19) has risen exponentially worldwide [1]. Multiple studies have demonstrated that immunocompromised patients may suffer from significant morbidity and mortality associated with COVID-19 [2,3,4]. Vaccination is recommended as a primary prevention method, but immunosuppressive treatment blunts the immune response leaving patients at higher risk of SARS-CoV-2 infection [1]. Moreover, SARS-CoV-2 has developed mutations throughout the pandemic, resulting in numerous viral variants of concern (VOCs) [5].

Several monoclonal antibodies (mAbs) targeting the SARS-CoV-2 spike protein have been authorized for the treatment of COVID-19 in high-risk patients. Previous studies demonstrated that the use of mAbs in immunocompromised patients was associated with lower hospitalization rates [6,7,8,9]. In addition, vaccinated transplant recipients with breakthrough COVID-19 benefitted from treatment with mAbs [10].

Tixagevimab with cilgavimab (tix-cil) is a combination of two long-acting mAbs blocking the viral spike receptor-binding domain that attaches to the human angiotensin-converting enzyme 2. In-vitro studies performed on SARS-CoV-2 Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) VOCs demonstrated that tix-cil had a >3,000-fold higher blocking affinity compared with other mAbs [11]. A phase III, double-blind, placebo-controlled study for pre-exposure prophylaxis demonstrated that patients receiving tix-cil had a relative risk reduction of 77% in the incidence of symptomatic COVID-19 [12].

Under an Emergency Use Authorization (EUA), tix-cil was authorized by the US FDA for pre-exposure prophylaxis in immunocompromised patients [13]. However, the efficacy of tix-cil in this high-risk population is unknown since the initial study included only a small number of immunocompromised patients. Moreover, its efficacy against the highly transmissible SARS-CoV-2 Omicron VOC (B.1.1.529) is unknown. In-vitro studies have shown that Omicron can escape humoral immune responses generated after natural infection or vaccination, and it is totally or partially resistant to neutralization by many mAbs due to its multiple spike protein mutations [5,14,15,16].

Given the imbalance between supply and demand, our institution prioritized the administration of tix-cil to high-risk patients with severe immunocompromising conditions (Supplementary material), as guided by the Minnesota Department of Health [17]. SARS-CoV-2 antibody levels were not used to prioritize allocation of tix-cil. Herein, we describe the clinical characteristics and outcomes of patients who developed COVID-19 following tix-cil administration.

Methods

This is a descriptive analysis of all patients who developed COVID-19 after receiving tix-cil during the first two months of the program at the Mayo Clinic in Rochester, Minnesota. The program is coordinated by a team of providers tasked with the equitable allocation of the limited drug supply. For this study, all patients who were 18 years or older and received the initially authorized dose of Tixagevimab 150 mg co-formulated with Cilgavimab 150 mg were included. Collected data included demographic characteristics, comorbidities, current immunosuppressive regimen, COVID-19 immunization status, clinical presentation, COVID-19 testing methodology, COVID-19

directed therapies, and clinical outcomes, including the need for supplemental oxygen and hospitalization. All data were retrieved from our electronic health records. For available samples, we performed genomic analyses to describe spike protein mutations and characterize specific VOC.

Patient Consent Statement

The Mayo Clinic Institutional Review Board approved the study protocol. Patient consent was waived.

Results

Of the 1,080 eligible immunocompromised patients, 674 patients (37% with hematological malignancies, 23% with autoimmune disease, 22% solid organ transplant recipients, 11% hematopoietic stem-cell transplant recipients, 7% with other immunocompromising conditions) received tix-cil during the first two months of our pre-exposure prophylaxis program. Eight patients (1.2%) were subsequently diagnosed with SARS-CoV-2 infection after receiving tix-cil. The characteristics of these patients are summarized in the Table.

Four patients were solid organ transplant recipients, three had underlying hematological malignancies, and one patient was an allogeneic stem-cell transplant recipient. Six patients had received three doses, while one had two doses of mRNA COVID-19 vaccines. One patient had not yet received any COVID-19 vaccine due to ongoing chemotherapy and then stem cell transplantation. All vaccinated patients were not tested for SARS-CoV-2 spike protein antibody after vaccination. None of the patients had a prior history of COVID-19.

SARS-CoV-2 infection occurred early after tix-cil administration, with varying clinical presentation. While most patients presented with mild respiratory symptoms, two patients were asymptomatic and diagnosed during screening before undergoing a procedure. The median time between tix-cil administration and the onset of symptoms was 2.5 days (range, 1-7 days). The diagnosis was confirmed by molecular testing in most patients.

Genomic analysis was planned for all patients, but samples were not available for seven patients (home antigen testing, n=2; molecular test done in external laboratory, n=3; cycle threshold too high for analysis, n=2). Only one sample was available for genomic analysis. The variant was found to belong to the Omicron sublineage BA.1 (Supplementary Figure).

Four patients received sotrovimab (500-mg infusion), and none of them progressed to severe COVID-19. Two asymptomatic patients were not eligible for sotrovimab treatment. Only two patients required hospitalization. One liver transplant recipient (Table, patient 1) presented with acute hypoxic respiratory failure requiring low-flow supplemental oxygen due to concomitant *Streptococcus pneumoniae* pneumonia, bacteremia, and empyema. The stem-cell transplant recipient (Table, patient 4) presented with *Campylobacter* enterocolitis and was hospitalized for persistent diarrhea due to coexisting acute graft-versus-host disease involving the gastrointestinal tract. None of the eight patients died by the time of this report (median follow-up, 99 days; range 66 – 108).

Discussion

This brief report describes our early experience with tix-cil for preventing COVID-19 among severely immunocompromised patients. Eight patients were diagnosed with COVID-19 within the first two weeks of receiving this medication. These infections could have been caused by acquisition of SARS-CoV-2 around the time (prior to or shortly after) of receiving prophylaxis. Tix-cil reaches maximum concentration in serum at a median time of 15 days [18]. We presume that the maximum benefit may not yet have been achieved to prevent COVID-19 in these severely immunocompromised patients. Moreover, all patients included in this analysis received the initially approved lower dose (tixagevimab 150 mg with cilgavimab 150 mg). The FDA subsequently recommended increasing the dose to 300 mg of tixagevimab and 300 mg of cilgavimab based on previous in-vitro studies showing that tix-cil has a substantial reduction in neutralizing activity against Omicron VOC [14,15,19]. After the EUA revision, we identified six additional patients who developed COVID-19 at a median time of 26.5 days (range, 6 – 32 days) following administration of the higher dose of tix-cil. These patients were asymptomatic or presented with mild respiratory symptoms. Most of them received bebtelovimab, and none required hospitalization. Genomic analysis of the variants infecting these six patients has not been performed.

Despite using the previously recommended lower tix-cil dose, only one patient required hospitalization due to respiratory failure caused by concomitant complicated invasive pneumococcal disease. None of the other patients required hospitalization. While four patients received rescue therapy with sotrovimab, we cannot exclude the possibility that tix-cil may have also prevented disease progression. Indeed, two asymptomatic patients

and one with mild symptoms did not progress to symptomatic COVID-19 despite not receiving sotrovimab. An ongoing clinical trial is evaluating the use of tix-cil to treat COVID-19 in adults in the outpatient setting [20].

Alternatively, the lack of progression to severe COVID-19 may have been due to an effective vaccination series. Most of our patients completed three-dose series of mRNA vaccines. Previous reports showed a protective effect of three doses of the COVID-19 vaccine against the Omicron variant compared with two or fewer doses. However, these reports have not included high-risk immunocompromised patients who do not mount protective levels of SARS-CoV-2 neutralizing antibodies [21]. Therefore, it is crucial for immunocompromised patients to continue using additional measures, such as masking, for protection against COVID-19.

The Omicron BA.1 variant was the most common circulating VOC in Minnesota (99.4%) during the time of our study [22]. Accordingly, four symptomatic patients were given sotrovimab rescue therapy. The lack of clinical progression of COVID-19 in these four patients correlated with studies that showed that sotrovimab retained neutralizing activity against the Omicron sublineage BA.1 [14,15,23]. SARS-CoV-2 genomic sequencing performed on one patient demonstrated an Omicron variant with multiple mutations in the spike protein. The analysis of the spike protein mutations predicted a reduced mAb activity, with a 75-fold reduction in the activity of tix-cil and only a 5-fold reduction of sotrovimab activity [24]. Accordingly, sotrovimab was administered in our patients with mildly symptomatic breakthrough infections after receiving tix-cil prophylaxis. However, sotrovimab is no longer recommended given its reduced in-vitro activity against the currently circulating Omicron BA.2 variant. Bebtelovimab was given to five more patients who developed COVID-19 after receiving the higher dose of tix-cil [25].

Despite the concerns about the effectiveness of tix-cil against SARS-CoV-2 Omicron VOC, 98.8% of our high-risk patients who received tix-cil did not develop COVID-19 by the time of this analysis. Most of the patients diagnosed with COVID-19 presented with mild disease, and none required mechanical ventilation or died. A recent study of 416 kidney transplant recipients reported that 9.4% developed COVID-19 after receiving tix-cil pre-exposure prophylaxis, including two patients who died [26]. The higher incidence of COVID-19 in this study can be related to differences in the population (our study only included 69 kidney transplant recipients), circulating SARS-CoV-2 VOCs, baseline immunosuppressive regimens, and use of mAb rescue therapy to prevent progression. A larger sample and longer follow-up will be needed to assess the real-world efficacy in specific groups of immunocompromised hosts.

Despite the potential protective effect conferred by tix-cil, our observations emphasize the need for additional prevention measures, such as masking and completing immunization series, while SARS-CoV-2 transmission remains high in the community.

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Potential conflicts of interest

Dr. Razonable has received grants from Regeneron, Roche, Gilead for research not directly related to this study (research funds were given to Mayo Clinic). Dr. Vergidis has received research grants from Scynexis and Cidara and has served on the DSMB for AbbVie, Vanda and Algernon Pharmaceuticals (all fees paid to Mayo Clinic). The other authors have reported no conflicts of interest.

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Legends

Table: Clinical characteristics of the eight patients how were diagnosed with COVID-19 after receiving tixagevimab-cilgavimab prophylaxis

Supplementary material. Immunocompromised conditions that were classified as highest risk (Category 1) and were prioritized for receiving Tixagevimab-Cilgavimab at our institution as guided by the Minnesota Department of Health: (https://www.health.state.mn.us/diseases/coronavirus/hcp/tigcilethical.pdf).

Supplementary figure. Genomic sequencing analysis (AmpliSeq SARS-CoV-2 Research Panel on the Genexus Integrated Sequencer) of the strain of SARS-CoV-2 detected in one of our patients using The Stanford Coronavirus Resistance Database (CoV-RDB; https://covdb.stanford.edu) [19]. The sequence analysis was compatible with SARS-CoV-2 Omicron variant, sublineage BA.1.

Table. Clinical characteristics of the eight patients how were diagnosed with COVID-19 after receiving tixagevimab-cilgavimab prophylaxis

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, years	24	87	43	67	73	49	65	21
Gender	Female	Male	Male	Female	Female	Female	Female	Female
Comorbidities	Diabetes, liver transplant	Chronic lung disease, DLBCL	DLBCL	Allo-SCT, diabetes	Cirrhosis, CKD, multiple myeloma	Heart and lung transplant, hypertension, obesity	Diabetes, hypertension, kidney and liver transplant	Heart and kidney transplant
Immunosuppressive regimen	Azathioprine, prednisone, tacrolimus	R-CVP	R-CHOP	Cyclosporine	Bortezomib, daratumumab, dexamethasone	MMF, prednisone, tacrolimus	MMF, prednisone, tacrolimus	Prednisone, tacrolimus
SARS-CoV-2 vaccine - Type - Number of doses	mRNA vaccine 3	mRNA vaccine 3	mRNA vaccine 2	None	mRNA vaccine 3	mRNA vaccine 3	mRNA vaccine 3	mRNA vaccine 3
Time between Tix/Cil and onset of COVID-19 symptoms, days	1	7	6	1	4	1	N/A	N/A
Time between Tix/Cil and COVID-19 diagnosis, days	4	8	7	12	6	3	4	4
SARS-CoV-2 test	PCR (external laboratory)	Home antigen test	Home antigen test	PCR (CT value 32.3)	PCR (external laboratory)	Home antigen test, PCR (CT value 22.6)*	PCR (external laboratory)	PCR (CT value 36.6)
Clinical presentation	Body aching, fever, rhinorrhea, dyspnea	Malaise, rhinorrhea	Malaise, rhinorrhea	Cough, diarrhea, malaise	Malaise, rhinorrhea	Cough, dyspnea, malaise	Asymptomatic	Asymptomatic
Complications	*S. pneumoniae* bacteremia, pneumonia, and empyema	None	None	*Campylobacter* sp. enterocolitis	None	None	None	None

COVID-19 directed therapy	Dexamethasone, remdesivir	Sotrovimab rescue therapy	Sotrovimab rescue therapy	Sotrovimab rescue therapy	None	Sotrovimab rescue therapy	None	None
Use of antibiotics	Ceftriaxone	None	None	Levofloxacin	None	None	None	None
Oxygen therapy	Low-flow supplementary oxygen	None	None	None	None	None	None	None
Clinical outcome	Hospitalization for management of hypoxia and infection	Outpatient symptomatic management	Outpatient symptomatic management	Hospitalization for management of persistent diarrhea	Outpatient symptomatic management	Outpatient symptomatic management	N/A	N/A
Mortality	No	No	No	No	No	No	No	No

*Patient initially tested positive at home but then had a molecular test when presented in the hospital complaining of cough and dyspnea. Abbreviations: Allo-SCT, allogenic stem-cell transplant recipient; CKD, chronic kidney disease; CT, cycle threshold; DLBCL, Diffuse large B-cell lymphoma; DKA, diabetes ketoacidosis; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; mRNA, messenger RNA; N/A, not applicable; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; PCR, polymerase chain reaction test.